In claim 5, line 1, replace "eukaryotic" with --mammalian--, in line 3, after "active", insert --heterodimeric--, and in line 8, after "vector", insert --the beta subunit being encoded by said first expression vector or a second expression vector--.

E1

In claim 29, line 2, replace "pRF375" with --pRF398--.

In claim 41, line 1, replace "34" with --33--.

R E M A R K S

The claims have been rejected under 35 U.S.C. §§112 and 103, and provisionally rejected under the judicially created doctrine of obviousness-type double patenting.

The §112 rejections are met by the present amendment, which cancels redundant claims, corrects errors in the claims pointed out by the Examiner, and also limits the claims, as required by the Examiner, to require that the expression system employed to make hormones according to the invention is a mammalian cell expression system.

The present application and copending application Serial No. 696,647, which the Examiner cited as the basis of a provisional obviousness-type double patenting rejection, are commonly owned, and applicants will file, at the appropriate time, a terminal disclaimer in compliance with 37 CFR 1.321(b).

Turning now to the §103 rejection based on the two FIddes et al. papers; Pierce et al.; Moriarty et al.; and Rice et al., the present amendment adds the host cell limitation as

suggested in the Office Action in connection with the §103 rejection (Office Action, p. 6, first full paragraph), and distinguishes Rice by requiring that both subunits be encoded by vectors (Office Action, p. 6, second full paragraph). Thus this amendment fully meets that rejection as to all claims except claim 46. Nonetheless, for the sake of completeness, the references are again discussed below.

At the outset it must be reiterated that none of the references of record even suggest, let alone achieve, applicants' invention, the production of a human fertility hormone in one cell transformed with DNA encoding both the alpha and beta subunits which are processed and assembled into a biologically functional dimeric hormone within that cell. This is so despite the fact that there has long been a need for a means of making pure hormones which can be used in controlled proportions to induce ovulation in infertile women (see the discussion of the Frustaci septuplets in a previous response). Applicants' pioneering work was not attempted, nor even suggested, by others in the field either because no one thought of the idea, or other workers assumed it would not work. Witness the two Fiddes papers, which show that, in 1981, cDNA's encoding both the alpha and beta subunits of hCG existed, and presumably could have been transformed into a eukaryotic cell, as applicants ultimately did, had anyone thought of doing so. Yet this was not done, despite the above-mentioned need.

The Examiner's attention is directed to the previously-submitted Pierce declaration, which counters the rejection over the Pierce et al. paper, and Moriarty et al. As the Pierce declaration pointed out, the Pierce et al. paper describes in vitro association work in which naturally occurring dimeric hormone, which had already been synthesized and properly folded and processed, was treated to cause disassociation and then allowed to reassociate, not within living cells, but in a test tube. This deficiency of the Pierce et al. paper is in no way alleviated by the teaching of Moriarty et al., which is simply to the effect that a recombinant mammalian cell is capable of glycosylating a protein encoded by a cDNA. Moriarty et al. deals only with a monomeric protein, and teaches nothing whatsoever about the ability of two different, separately-encoded protein chains to associate in a cell to form a biologically functional dimer.

Nor does Rice et al. make up for the deficiency of the Pierce et al. paper. Rice et al., unlike the invention as now claimed (see amendment to claim 5), involves a recombinant cell in which one of the two chains of a dimer (the heavy chain of an antibody) is already being produced by the cell prior to transformation with DNA encoding the light chain. The fact that functional antibody was produced by such cells is in no way predictive that a cell, in which both chains are encoded by recombinant DNA molecules, will produce a dimer in which the chains properly associate and which is biologically functional.

Turning now to the rejection of claim 46, directed to a cDNA sequence encoding the beta subunit of human LH, reconsideration of this rejection is requested. The Examiner states that the high degree of homology (82%) between the beta subunits of hCG and LH would render routine the isolation of the cDNA for the LH beta subunit from pituitary tissue, using a homologous hCG probe. Although it is true that, generally speaking, this strategy does work, and in fact was used by applicants, it was not obvious, prior to that work, that the approach would succeed. First, the 82% homology referred to by Fiddes et al. is amino acid homology, not nucleic acid homology which, because of the redundancy of the code, is substantially lower than 82% (probes, of course, are nucleic, not amino, acids). If a region which is not homologous (e.g., the carboxy terminus) is used, the beta subunit of hCG, (also present in pituitary tissue) not of LH, will be obtained. And even if a region which is homologous is used, the wrong result can be obtained. As is discussed in the Pierce et al. paper of record, the beta subunits of the hormones hCG, LH, FSH, and TSH all share a common Cys-rich determinant loop region, and a probe to this region could as easily select the beta subunit of hCG, FSH, or TSH as LH. Thus the information in the Fiddes et al. papers, while suggestive of a strategy for obtaining the cDNA for the LH beta subunit, is far from a disclosure of a particular probe which would work, and in fact could easily

lead to the use of many probes which would not work. The obviousness rejection of claim 46 should be withdrawn.

In view of the above, it is submitted that all of the claims in the application are in condition for allowance, and such action is requested.

Respectfully submitted,

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